Award Number: W81XWH-09-1-0092

TITLE: Telepharmacy Robotic Medicine Delivery Unit

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CONTRACTING ORGANIZATION:

INRange Systems, Inc.
Altoona, PA 16602

REPORT DATE: December 2009

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	**2. REPORT TYPE**	**3. DATES COVERED** *(From - To)*
01-12-2009	Annual	26 Nov 2008 - 25 Nov 2009

4. TITLE AND SUBTITLE
TelePharmacy Robotic Medication Delivery Unit

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-09-1-0092

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
INRange Systems Inc.

Altoona PA 16602-5944

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, MD 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for public release; distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

The military has an increasing number of patients with combat-related impairments that contribute to suboptimal medication self-management. These impairments include TBI, PTSD, polytrauma, and mental health issues. A significant number of these patients are in transitional care outpatient settings, lacking adequate clinical staff to provide the necessary pharmacy services. The objective of this study is to evaluate whether the use of a telepharmacy robotic remote medication dispensing unit (TRMDU), in addition to medication review in patients assigned to WTUs, VA hospitals, and similar units, leads to improved outcomes and reduced health care costs for patients when compared with medication review alone. This study will use a prospective non-randomized repeated measures design with two sites using a control condition for 12 weeks, followed by a 12-week TRMDU intervention condition. The third site will serve as intervention only.

15. SUBJECT TERMS
No subject terms provided.

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			USAMRMC
U	U	U	UU	12	**19b. TELEPHONE NUMBER** *(include area code)*

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

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INTRODUCTION

This study involves a FDA cleared remote medication management device, 21 CFR 880.6315, that provides unit dose delivery of medications across the continuum of care. The Telepharmacy Robotic Medication Dispensing Unit (TRMDU), developed by INRange® Systems, Inc., is a Class II medical device, located in the home, outpatient setting, or in the field, and consists of a medication delivery unit and two-way communication software that allows a health care professional to remotely manage prescriptions stored and released by the patient-operated delivery unit. The delivery unit is approximately the size of a bread box, and it plugs into a standard power outlet.

We have continued to develop the protocol that will assess this TRMDU unit in subjects with traumatic brain injury (TBI), post-traumatic stress disorder (PTSD), multiple traumatic brain injury (MTBI), or polytrauma. The objective of this study is to evaluate whether use of a TRMDU, in addition to medication review in patients assigned to WTUs, VA hospitals, and similar units, leads to improved outcomes and reduced health care costs for patients when compared with medication review alone.

BODY

Study Team Selection and Basic Study Design (Dec. 2008-May 2009)

The original proposal called for the evaluation of study subjects with traumatic brain injury (TBI), post-traumatic stress disorder (PTSD), multiple traumatic brain injury (MTBI), or polytrauma receiving the TRMDU to be assessed for a number of outcomes. The study methods were further developed between November 2008 and May 2009 to include a prospective evaluation and a control group. An advisory panel, consisting of members from the Army, Navy, Air Force, representatives from INRange, other contractors, and study investigators was formed to assist in the initiation of the study and interpretation of the results. This advisory panel met once in Fall 2008 and three times in 2009 (Spring, Summer, and Fall). There was a change in the Principal Investigator in May 2009, from Mary Ann Papp (INRange and Wisconsin College of Medicine) to the co-PI's Daniel Touchette, Pharm.D (University of Illinois at Chicago) and Jill Winters, PhD, RN (Columbia College of Nursing).

Study outcomes were determined and agreed upon by May 2009. These outcomes will be assessed through the following aims: 1) To evaluate the impact of point-of-care medication delivery systems by means of TRMDUs on medication adherence, drug related problems (DRPs), admissions to the hospital, and emergency department visits; 2) To evaluate the impact of using TRMDUs on patient pain, psychological well-being, and health-related quality of life (QOL); 3) To evaluate the impact using TRMDUs has on cost of care. This study will use a prospective non-randomized repeated measures design with two sites using a control condition for 12 weeks, followed by a 12-week TRMDU intervention condition. The third site will serve as intervention only. The primary outcome for the study will be Drug-Related Problems (DRPs) identified after 12 weeks of TRMDU use. Secondary outcomes will include pain, psychological well-being, health-related QOL, and cost of care.

Study Site Recruitment, Site Visits, and Protocol Development (May 2009 – Aug 2009)

After assuming the co-Principal Investigator roles in May 2009, Daniel Touchette and Jill Winters travelled to each of the identified program sites where a series of meetings were held with site investigators. The program implementation and evaluation will be conducted at three sites: 1) James A. Haley VA Hospital and Polytrauma Facility in Tampa Bay, Florida (Tampa VA); 2) Naval Hospital Camp Pendleton, in Camp Pendleton, California (Camp Pendleton); and 3) Ireland Army Community Hospital, Fort Knox, Kentucky (Fort Knox).

During these site visits, meetings were held to discuss each site's interest in and ability to enroll both control and intervention subjects; potential number of enrollees possible; current medication reconciliation practices; feasibility of recruitment and screening procedures; data collection; and issues that might be problematic to conduct of the study.

After completion of all site visits, changes were made to the protocol to incorporate evidence based literature and comments and suggestions from each of the sites. Also, study procedures were made more explicit.

In brief, the Tampa VA will serve as an intervention only site, while Camp Pendleton and Fort Know will serve as a control followed by intervention sites. We estimate that approximately 30 intervention study subjects will be enrolled at Tampa VA; 15 control and 15 intervention subjects at Camp Pendleton; and 20 control and 20 intervention subjects at Ft. Knox. Additional sites will be recruited, as needed, to ensure that sample size requirements for the study are met.

For this study, medication reconciliation is defined as a process of building a complete medication list, based on the most current information taken from prescription bottle directions, patient interview, and medical record information, with the goal of reducing medication errors. Medication reconciliation (and subsequent collection of the medication list for assessment of DRPs) will be done within one week of subject enrollment in the study. Discrepancies and other DRPs will be brought to the attention of the prescriber, and if appropriate, changes will be made to the existing medication regimen.

Subject selection was updated based on input from each of the site investigators and information on subject ability to complete the study's subject assessment forms. The resulting inclusion and exclusion criteria are as follows:

1) At least 18 years of age
2) Alert and oriented to person, place, and time
3) Primarily use English language for written and oral communication
4) Have a diagnosis of Traumatic Brain Injury (TBI), Multiple Traumatic Brain Injury (MTBI), Post-Traumatic Stress Disorder (PTSD), or Polytrauma.
5) Receiving treatment for chronic pain management
6) Taking least 4 chronic prescription medications
7) Living in a participating WTU (or similar unit such as a WWB) or enrolled in the Tampa Veterans Administration polytrauma outpatient treatment facility at the time of enrollment
8) Achieve a minimum score of 24 on the Mini-Mental State Examination (Folstein 1975) [See Appendix E]

Participants will not be enrolled in the study if they meet the following exclusion criteria:

1) Disabilities preventing safe use of the TRMDU (e.g., blindness, amputation, paralysis)
2) Projected life expectancy of less than 3 months

Once a subject is enrolled in the study, he or she will remain in the study until the final evaluation has been completed (unless the subject chooses to withdraw or is withdrawn by the lead investigator for protocol violations), even if the subject no longer meets inclusion criteria (e.g., number of medications drops to less than four).

Final Protocol Development (Jul 2009 – Sep 2009)
The study investigators then, in consultation with biostatisticians from the University of Illinois at Chicago and the Columbia College of Nursing, with input from the study's advisory board, refined study methods and data analyses. The estimated necessary sample size was determined to be 110 subjects in the intervention arm and 55 in the control arm. Analysis plans for each study arm were outlined in detail and the data collection plan for Aim 3 (costs) was further elucidated. These are as follows:

For the analyses, data will be collected from two main sources: 1) information collected from medication reconciliation interviews and 2) information collected from Tricare and Veterans' Administration databases. Data collected at each program site will be de-identified, forwarded to, and stored at the University of Illinois at Chicago (UIC) or Columbia College of Nursing (CCON) for analyses. Data collected for the purposes of patient care only will not be forwarded to UIC or CCON. Data forwarded to UIC and CCON for analyses by the respective study sites will include demographic data collected at baseline (gender, date of birth, race, ethnicity); inclusion criteria and relevant medical problems (e.g., TBI, chronic pain, PTSD, major affective disorder, etc.) at baseline; and medical history from patient medical records (electronic where available) at baseline. Other data that will be forwarded and stored include lists of medications identified by the pharmacist's medication reconciliation at baseline, one, two, and three months post-enrollment; pill counts of all chronic prescription medications monthly for three months post-enrollment (to assess adherence); type, strength, number of narcotic tablets monthly for three months post-enrollment; and patient questionnaires completed at baseline, one, two, and three months post-enrollment. In addition, hospital and emergency department admissions (from study enrollment to 3 months post-enrollment and medical and prescription fill data will be requested under a data use agreement prepared post-approval by each site's IRB (for Camp Pendleton and Fort Knox) or the R&D committee (for the Tampa VA). Data will be obtained from the MDR or M2 data warehouses for Camp Pendleton and Fort Knox subjects, and data will be collected from the Tampa VA data repository for VA subjects. More specifically, the following or similar data elements will be requested from study enrollment to 3 months post enrollment:

I. All prescription fills for the period of the study
   a. Drug name and DIN
   b. Dose strength
   c. Dosage form
   d. Number of tablets / other
   e. Days supplied (if available)
   f. Sig (if available)
   g. "Amount billed" (if applicable)

h. "Amount reimbursed" (if applicable)
i. "Location filled" (if available) – i.e. was the prescription filled at the military base site or at a community pharmacy, or other?
j. Date filled

II. All medical claims data for the period of the study
a. Date of visit / discharge
b. Visit type (this includes hospitalization, ED visit, clinic visit, office visit, telephone consultation, other consultation for all provider types)
c. ICD-9 codes
d. DRG
e. Procedure codes (HCPCS)
f. Location (military, VA, non-military site)
g. "Amount billed" (if applicable)
h. "Amount reimbursed" (if applicable)

Outcomes

1.1 Adherence

Adherence will be determined for both groups by prescription refill records and pill counts [See Appendix F]. Adherence will be estimated using the medication possession ratio (MPR). A modified MPR will be calculated as follows:

$$\frac{\text{Days of medication supplied during enrollment - Days supply remaining (pill count)}}{\text{Enrollment days}}$$

Analysis plan: Comparisons of the modified MPR will be made between the intervention and control participants using GLMM at 3 months post-enrollment.

Patient reported adherence also will be estimated for both groups using an 8-item Morisky adherence questionnaire [See Appendix H]. The 8-item Morisky Medication Adherence Scale (MMAS) has been validated in patients with hypertension and correlates with blood pressure.(Morisky, Ang et al. 2008) The tool was selected because it is easy for subjects to complete and has high sensitivity (93%) and good specificity (81%) compared with other measures (Svarstad 1999; Morisky 2008). It's psychometric properties also have been assessed in subjects with diabetes (Sakthong 2009) and against pharmacy refill records (Krousel-Wood 2009).

Analysis plan: Comparisons in the MPR will be made between the intervention and control subjects. A GLMM will be employed, adjusting for baseline differences in the site and for individual study participants. Comparisons in the MPR will be made between the intervention and control subjects. A GLMM will be employed, adjusting for baseline differences in the site and for individual study participants.

1.2 Drug-Related Problems (DRP)

DRPs will be defined according to the Pharmaceutical Care Network Europe (PCNE) Classification. Specifically, they are defined as an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes (van Mil 2004). Although not

explicitly stated in the PCNE Classification, the operational definition will include not only those events or issues related to drug administration, but also events or issues related to a lack of necessary drug therapy [See Appendix I].

Upon enrollment, medication reviews will be conducted with all participants, using the "Brown Bag" review (Nathan 1999) [See Appendix J]. Medication lists and pharmacist notes documenting DRPs identified will be collected through chart review for 3 months after enrollment in the study (i.e., TRMDU introduction or control condition). A study investigator, blinded to subject location or group assignment (i.e., experimental or control), will assess participant medication lists for potential DRPs. This investigator will classify the DRPs according to the PCNE classification. The number and types of DRPs will be collected.

Analysis Plan: DRPs will be summarized using the PCNE classification (type of DRP) for each of the two groups according to the type of DRP. The primary endpoint will be number of DRPs between the intervention and control groups. A GLMM (Poisson) will be employed, adjusting for baseline differences in the site and for individual study participants. A secondary analysis will be conducted comparing the time exposed to DRPs between the two groups. A Cox proportional hazard model will be employed, again adjusting for baseline differences by site and individual.

1.2 and 1.3 Hospital and Emergency Department Admissions

The number of hospital and emergency department (ED) admissions will be collected from the DOD administrative health claims data.

Analysis Plan: Comparison of the number of ED visits and hospitalizations observed in each study arm will be made at baseline, one, two, and three months post-enrollment. A GLMM, Poisson will be employed, adjusting for baseline differences in the site and for individual study participants.

1.4 Narcotic Prescription Exposure

It is anticipated that duplicate prescriptions will be reduced by use of the TRMDU. The numbers of different narcotic medications participants are taking, and the number of pills dispensed for the duration of study enrollment will be determined using prescription dispensing records and pill counts. Narcotic prescriptions will be converted to equivalent doses using an analgesic equivalent dose chart and the total dose received will be compared at one, two, and three months post-enrollment [See Appendix G] .

Analysis Plan: Comparison of the number of narcotic prescriptions filled and analgesic equivalent dose observed in each study arm will be made at baseline, one, two, and three months post-enrollment. A GLMM, Poisson will be employed, adjusting for baseline differences in the site and for individual study participants.

1.5 Number of Medication Reconciliations Conducted

The number of medication reconciliations conducted by the study site pharmacist in the three month study will be documented for each study subject. The reason for the medication reconciliation will also be documented (e.g., serious adverse drug event, hospitalization, emergency department visit).

Analysis Plan: Comparison of the number of narcotic medication reconciliations required per study subject will be made at six months post-enrollment. A GLMM, Poisson will be employed, adjusting for baseline differences in the site and for individual study participants.

2.1 Pain

Pain control will be assessed by means of the Short-Form McGill Pain Questionnaire (SF-MPQ) (Melzack 1987). It is a valid and reliable instrument for measuring pain, and it has been used with TBI and PTSD in the past (Cantor 2008). It consists of 15 pain descriptors (11 sensory, 4 affective) that are rated by the subjects on a 4-point intensity scale (0=none to 3=severe), reflecting the level of pain over the past week. Three scores are derived: (1) sensory score, (2) affective score, and (3) total score [See Appendix K].

Analysis Plan: Comparisons of sensory, affective, and total pain scores will be made between the intervention and control participants using GLMM at baseline, one, two, and three months post-enrollment.

2.2 Psychological Well-Being

Psychological well-being will be measured by means of the Profile of Moods Brief Scale (POMS-Brief) (McNair 1992). The POMS-Brief, developed from the longer 65-adjective POMS, is a commonly used measure of psychological distress and has been found to be particularly useful in measuring changes in mood over time and therefore is appropriate for use in this longitudinal study. The 30-adjective POMS-Brief examines the same six mood states of the longer POMS: (1) Tension-Anxiety, (2) Depression-Dejection, (3) Anger-Hostility, (4) Vigor-Activity, (5) Fatigue-Inertia and (6) Confusion-Bewilderment. Scores for each of the six subscales range from 0–20 with higher scores indicating higher distress except for the subscale of Vigor-Activity which is negatively scored. A total mood score is obtained by adding the scale scores of Tension-Anxiety, Depression-Dejection, Anger-Hostility, Fatigue-Inertia, and Confusion-Bewilderment and subtracting the scale score of Vigor-Activity. The total mood score ranges from 0–80 (from least disturbed to most disturbed). According to the POMS Manual, internal consistency estimates for the POMS were found to be satisfactory nearing .90 or above (McNair 1992)[See Appendix L].

Analysis plan: Comparisons in the six subscales and total mood score will be made between the intervention and control participants using GLMM at baseline, one, two, and three months post-enrollment.

2.3 Health-Related Quality of Life

Health-Related QOL will be measured by means of the Short-Form 36 (SF-36) (Ware 1993). The SF-36 QOL questionnaire assesses 8 domains of general health from the patient's perspective: (1) physical functioning, (2) role limitations caused by physical health problems, (3) bodily pain, (4) general health, (5) vitality, (6) social functioning, (7) role limitation caused by emotional problems, and (8) mental health. It has been validated through numerous studies worldwide for use in a variety of health states [See Appendix M].

Analysis plan: Comparisons in the eight domains and total score will be made between the intervention and control participants using GLMM at baseline, one, two, and three months post-enrollment.

3.1 - 3.3 Medication, Medical, and Total Cost of Care

The cost analysis will be conducted from the military's perspective. Six-month medication and medical cost of care will be extracted from the DOD prescription and medical claims databases. Time to complete medication reconciliation will be collected using a pharmacist self-report measure.

Analysis plan: Comparisons in the costs of care will be made between the intervention and control subjects. A GLMM, loglinear transformation will be employed, adjusting for baseline differences in the site and for individual study participants.

IRB Preparation and Application (Aug 2009 – Dec 2009)

The processes for data acquisition from TRICARE were determined and the approval process was begun. The protocol was submitted to Jeffrey Stephenson for preliminary review and comment prior to submission to the University of Illinois at Chicago for review. The IRB documents are currently being prepared for the first site, Fort Knox (to be submitted to the Walter Reed IRB), and for the Columbia College of Nursing. Once approval has been obtained from these three sites, the protocol will go for a second level review to Fort Detrick. Finally, approval will be sought from the final two sites, Camp Pendleton (through Balboa Naval Hospital) and the Tampa VA.

Also, a CRADA was requested by Camp Pendleton, outlining the staffing requirements for the study. This CRADA, between TATRC, INRange, and Camp Pendleton, is currently under review by the Commanding Officer at Camp Pendleton.

KEY RESEARCH ACCOMPLISHMENTS

To date, considerable progress has been made in the following areas:

- Preparing the protocol
- Obtaining required approvals
- Identification and gaining support of the participating sites
- Preparation of the IRB documents

REPORTABLE OUTCOMES

We are currently completing the development phase of the study. At present there are no reportable outcomes. We expect that, when completed, this study will generate at least one and possibly two manuscripts on the effectiveness of the TRMDU on adherence and outcomes assessed in this study for this population. Publication of these manuscripts will be pursued in major, peer-reviewed medical journals.

CONCLUSION

Findings from several studies have shown that better medication adherence leads to better outcomes, fewer hospitalizations and emergency department visits, and greater QOL. Use of the TRMDU may improve medication adherence; reduce DRPs; and positively impact pain, psychological, and QOL measures for veterans with TBI, PTSD, and/or polytrauma. In addition, health care costs and hospitalizations may be reduced. If findings from this study support the hypotheses, use of the TRMDU may be a valuable intervention and lay the groundwork for applications of the TRMDU with this population in both the Warrior Transition Units and in community settings. In addition, those individuals in rural settings with limited access to major medical centers and other populations with documented difficulty with medication adherence may benefit from such a device. This study will serve to lay the groundwork for additional funding to assess the effectiveness of the TRMDU in these settings.

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